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10/681,490	10/07/2003	Gilbert Thill	G-099US03DIV	7137

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	
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05/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TK

Office Action Summary	**Application No.** 10/681,490	**Applicant(s)** THILL, GILBERT	
	Examiner Juliet C. Switzer	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 26 February 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15-18 and 20-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-18 and 20-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/26/07 has been entered.

Claim Rejections - 35 USC § 112

2. Claims 1, 6, 7 , 8, 9, 10, 24, 25, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a single stranded region "that is an insertion, deletion, or replacement," however, it is not clear how a single stranded region can be a deletion. In a heteroduplex, if there is a single stranded region it could result from the deletion of one segment of DNA relative to another, but it is not clear how the single stranded region itself is a deletion. Claims which depend from claim 1 are also indefinite for this recitation.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34, 35, 37, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the specification illustrates and discusses imperfect duplexes having a single stranded tail (see Figure 4, for example), the specification examiner was unable to identify discussion as to the length of the tail. Each of the rejected claims recites a particular length for the single stranded tail. Therefore, the claims are rejected for having new matter.

Claim Rejections - 35 USC § 103

5. Claims 1-12, 15-18, 20-32 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 5376526) in view of Wickermasinghe et al. (Biochimica et Biophysica Acta, 607 (1980) 411-419), and optionally further in view of Wilkin et al. (American Journal of Medical Genetics, Volume 85, pages 105-112, July 1999).

Brown et al teach a method which comprises the selection or isolation of heteroduplexes containing at least on internal single stranded region with a single stranded trap that involves the use of a recognition element that is benzoylated-naphthoylated-DEAE-cellulose (BNDC). Namely, Brown et al. teach the isolation of partially single stranded DNA from fully duplex DNA by using BNDC (see for example, Col. 7, lines 10-15; Col. 12, line 65-Col. 13, line 9). Brown et al. teach that under some circumstances it is desirable to isolate and map regions of the genome that represent differences between samples (Col. 3, 1st ¶; Col. 9, lines 9-25), and Brown et al. teach that genetic regions isolated by their methods may be cloned and analyzed for use in future diagnostic methods (Col. 8, lines 62-68). In the methods taught by Brown et al., heteroduplexes are formed between related DNA molecules (Col. 11, line 50- Col. 12, line 28), and the internal single stranded regions represent nucleotide differences between the two samples (Col. 6, line 67-Col. 7, line 9).

Regarding claim 2, Brown et al. teach a method which includes the steps of (a) obtaining a DNA sample containing related DNA molecules (Col. 3, lines 15-65); (b) denaturing the molecules (Col. 4, line 56); (c) annealing the denatured molecules to allow the formation of heteroduplexes (Col. 4, line 57; Col. 6, line 67-Col. 7, line 9); and (d) isolating or selecting the heteroduplex containing at least on single stranded region using a single-stranded trap comprising a recognition element that is BNDC (see for example, Col. 7, lines 10-15; Col. 12, line 65-Col. 13, line 9).

Independent claim 1 sets forth that the internal single stranded region is of at least 15 nucleotides in length, and independent claim 2 recites that the difference is at least 6 nucleotides or at least 15 nucleotides. The differences in the complex genomic hybridizations taught by Brown et al. would inherently comprise insertions and deletions of these lengths. Brown et al. specifically teach comparing eukaryotic genomes (in particular human genomes of high complexity (Col. 3, near line 40)), the comparison of these two genomes would necessarily result in single stranded regions of 15 or more nucleotides since relative to one another any two human genomes would contain pseudogenes, deletions, translocations, gene homologues, gene loss events, rearrangements, flipping of genes, etc. Thus, the comparison of two genomes as set forth by Brown et al. inherently and necessarily would have resulted in the production of heteroduplexes with nucleic acid differences of at least 6 or at least 15 nucleotides, and would have included deletions, insertions, and substitutions relative to one another (claim limitations 24-30).

Regarding claim 3, the Brown et al. teaches reducing the size of the DNA molecules (Col. 4, lines 15-40; Col. 9, lines 25-35; Col. 11, lines 35-40).

Regarding claim 4, Brown et al. teach removing single stranded unannealed DNA (Col. 5, lines 15-18; Col. 12, lines 34-44), and teach ligating adaptors to flush ended heterohybrids (Col. 5, lines 47-51).

Regarding claims 6-9 and 15-18, 31, and 32, Brown et al. teach that the nucleic acid samples can be from a single individual (i.e. single source, Col. 3), from different individuals (i.e. at least two different sources, Col. 3, lines 62-68), that the source will be genomic DNA, which inherently "comprises" cDNA fragments. Regarding claims 9 and 18, any genome has a "limited set of genes" since the total number of genes, even in a very large genome has a "limited" number of genes (as opposed to an infinite number of genes).

Regarding claim 10, Brown et al. teach mixing the sample with BNDC to the binding of the partially single stranded molecules (i.e. those molecules having internal single stranded regions) with the BNDC, formation of complexes and separation of the complexes by centrifugation or other means (Col. 7, lines 10-19; Col. 12, line 65-Col. 13, line 9).

Brown et al. do not teach a method wherein heteroduplexes are eluted from the single stranded trap. Brown et al. do not specifically teach, however, a method in which the molecules having single stranded regions are isolated on the BNDC are recovered and used in further analysis.

Wickermasinghe et al. teach that affinity chromatography on BNDC permits fractionation of fully double-stranded DNA from partially single-stranded DNA and exemplify methods wherein partially single-stranded DNA is eluted from a BNDC column separately from double-stranded DNA (p. 412, 1st full ¶ and p. 413, lines 2-3). Further regarding claim 11, Wickermasinghe et al. teach preparing a column with BNDC, washing the column with a buffer (i.e. equilibrating the column in a buffer), bring the column into contact with the sample to allow binding of molecules with single stranded regions and formation of complexes between the heteroduplexed molecules and the BNDC, and eluting DNA from the column (p. 412-413, heading "*Affinity chromatography on benzyolated naphthoylated DEAE-cellulose*"). During the elution of DNA from the column, DNA which are not bound to the column under elution conditions are removed from the column. Regarding claim 12, Wickermasinghe et al. teach washing the column with a buffers comprising 1M NaCl (p. 413). Regarding claim 21, the elution results in recovering the DNA from the complexes (p. 413).

Thus, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Brown et al. so as to have separately eluted the nucleic acids containing single stranded regions from the BNDC columns used by Brown et al., using methods as demonstrated by Wickermasinghe et al. One would have been motivated to isolate the heteroduplexed molecules by the express teaching of Brown et al. that the BNDC column separates partially single stranded molecules from fully duplexed DNA (Col. 7, lines 10-13) and that an embodiment of genetic mapping looks to differences within genomes (Col. 3, 1st ¶; Col. 9, lines 9-25). Further, one would have been motivated to use a method wherein the heteroduplexes are eluted from the BNDC column by the success of

Wickermasinghe et al. at using this method for the elution of such molecules, and in order to obtain the molecules which are bound to the BNDC in the methods taught by Brown et al. (see Col. 7, lines 10-19).

Brown et al. in view of Wickermasinghe et al. do not exemplify methods wherein the heteroduplexes are amplified, cloned or sequenced. However, given the express teachings of Brown et al. that under some circumstances it is desirable to isolate regions with nucleotide differences for further study, and the express suggestion by Brown et al. that sequences isolated should be cloned for further study, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of Brown et al. so as to have recovered and cloned the nucleic acids with single stranded regions taught by Brown et al. One would have been motivated to recover these nucleic acids for the purpose of further study of genomic regions with nucleic acid differences. Brown et al. do not teach the steps of amplifying DNA with differences, repeating the isolation of molecules with single stranded regions, or of sequencing the DNA harboring differences. However, at the time the invention was made, each of these methodologies was routinely practiced in the prior art for the isolation, cloning, and study of nucleic acid sequences of interest. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Brown et al. to include any of these steps for the enrichment of the nucleic acids having single stranded regions that represented sequence differences taught by Brown et al. Thus, in light of the disclosure of Brown et al., the claimed invention is prima facie obvious.

Although the nucleic acid differences of at least 15 nucleotides required by all of the instantly rejected claims are inherent to the methods taught by Brown et al. in view of

Wickermasinghe et al., an additional reference and motivation is also provided as an alternative to the rejection. Brown et al. in view of Wickermasinghe et al. do not expressly teach isolating or selecting heteroduplexes which comprise nucleic acid differences of fifteen or greater nucleotides. Brown et al. does expressly suggest using their methodologies to identify genetic regions of non-identity that are related to disease.

Wilkin et al. teach the formation of heteroduplex molecules from DNA samples of patients having kniest dysplasia, and the identification of heteroduplex molecules having deletions of greater than fifteen nucleotides (p. 108, Table 1). Furthermore, after identifying the regions with differences, the PCR products were purified and sequence or cloned into a plasmid vector (p. 109). Thus, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Brown et al. in view of Wickermasinghe et al. so as to have applied them to genomic DNA from patients having kniest dysplasia. One would have been motivated to study the genomes of individuals having this disease in order to isolate and identify nucleic acid differences related to disease.

6. Claims 1-2, 5-6, 8-9, 11-12, 15, 17-18, 20-23, 36, and 39, are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (Gene, 1997, 198:1-4) in view of Wickermasinghe et al. (Biochimica et Biophysica Acta, 1980, Volume 607, pages 411-419).

Regarding claims 1 and 2, Robinson et al. teach a method of isolating related DNA molecules harboring nucleic acid differences in a DNA sample, namely alternatively spliced RUSH mRNA wherein said method comprises the selection of isolation of heteroduplexes containing at least one single stranded region of at least 15 nucleotides. The single stranded region is a 57 base pair exon that is inserted in one sequence relative to another, or can also be described as deleted from one sequence relative to another. The region is also interpreted as a substitution in one strand relative to another since in one strand the 57 base pair region is substituted for a different particular nucleotide sequence. Robinson et al. teach eluting and recovering the heteroduplexes using HPLC. The column used in HPLC is "a single stranded trap" because it traps the heteroduplex molecules which have a partially single stranded region and elutes them at a different time than the perfectly annealed molecules (Figure 2B).

Regarding claim 3, Robinson et al. teach PCR amplification of a portion of the transcribed cDNA, and so this results in reducing the size of the DNA molecules.

Regarding claims 6 and 15, in each assay the total RNA was extracted from tissues of a sexually mature male or female rabbit, thus, is from a single source (Table 1).

Regarding claims 8, 17, the DNA sample comprises cDNA.

Regarding claims 9, 18, 30, 32, the DNA sample comprises cDNA molecules derived from the RUSH gene, and regarding claims 31 and 33, these are splicing isoforms of the RUSH gene.

Regarding claims 36 and 39, the annealed cDNA molecules are imperfect cDNA molecules that have no single stranded tail at both ends and one or more single stranded region of at least 15 nucleotides (Figure 1).

Robinson et al. do not teach a column that is packed with BNDC.

Wickermasinghe et al. teach that affinity chromatography on BNDC permits fractionation of fully double-stranded DNA from partially single-stranded DNA and exemplify methods wherein partially single-stranded DNA is eluted from a BNDC column separately from double-stranded DNA (p. 412, 1st full ¶ and p. 413, lines 2-3). Further regarding claim 11, Wickermasinghe et al. teach preparing a column with BNDC, washing the column with a buffer (i.e. equilibrating the column in a buffer), bring the column into contact with the sample to allow binding of molecules with single stranded regions and formation of complexes between the heteroduplexed molecules and the BNDC, and eluting DNA from the column (p. 412-413, heading "*Affinity chromatography on benzyolated naphthoylated DEAE-cellulose*"). During the elution of DNA from the column, DNA which are not bound to the column under elution conditions are removed from the column. Regarding claim 12, Wickermasinghe et al. teach washing the column with a buffers comprising 1M NaCl (p. 413). Regarding claim 21, the elution results in recovering the DNA from the complexes (p. 413).

Thus, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Robinson et al. so as to have used a BNDC column to separate the molecules having partially single stranded regions using methods as demonstrated by Wickermasinghe et al. One would have been motivated to modify the methods taught by Robinson et al. by the express teaching of by the teachings of Wickermasinghe et al. who teach that a BNDC column can accomplish this end, and in order to provide additional reagents and methods for isolating heteroduplex splice variants as taught by Robinson et al. Further, one would have been motivated to use a method wherein the heteroduplexes are eluted from the BNDC column by the success of Wickermasinghe et al. at using this method for the elution of such molecules.

Robinson et al. in view of Wickermasinghe et al. do not exemplify methods wherein the isolated heteroduplexes are amplified, cloned or sequenced, and Robinson et al. in view of Wickermasinghe et al. do not teach the repeating the isolation of molecules with single stranded regions. At the time the invention was made, each of these methodologies was routinely practiced in the prior art for the isolation, cloning, and study of nucleic acid sequences of interest. However, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of Robinson et al. so as to have recovered and cloned, amplified or sequenced the nucleic acids with single stranded regions taught by Robinson et al. One would have been motivated to recover these nucleic acids for the purpose of further study of genomic regions with nucleic acid differences, and amplification, sequencing, and cloning were all methods routinely used in the prior art for the study of nucleic acid molecules of interest. It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Robinson et al. to include any of these steps for the enrichment of the nucleic acids having single stranded regions that represented sequence differences taught by Robinson et al.

Conclusion

7. No claim is allowed.

8. All previously set forth arguments have been addressed in previous office actions. No new arguments were set forth with the filing of the RCE.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

May 8, 2007